Smith Sarah (Orcid ID: 0000-0002-2553-8494)
Aravamuthan Bhooma (Orcid ID: 0000-0003-0205-2149)

Title: Adults with cerebral palsy require ongoing neurologic care: A systematic review

Authors:

Sarah E. Smith
Email: sarah.e.smith@wustl.edu
Affiliation: Washington University School of Medicine, St. Louis, MO, USA

Mary Gannotti, PT, PhD
Email: gannotti@hartford.edu
Affiliation: University of Hartford, Shriners Hospitals for Children, Cerebral Palsy Network

Edward A. Hurvitz, MD
Email: ehurvitz@med.umich.edu
Affiliation: Department of Physical Medicine and Rehabilitation, Michigan Medicine/University of Michigan

Frances E. Jensen, MD
Email: frances.jensen@uphs.upenn.edu
Affiliation: Department of Neurology, Perelman School of Medicine, University of Pennsylvania

Linda E. Krach, MD
Email: lkrach@gillettechildrens.com
Affiliation: Gillette Children's Specialty Healthcare; Department of Rehabilitation Medicine University of Minnesota

Michael C. Kruer MD
Email: mkruer@phoenixchildrens.com
Cerebral Palsy & Pediatric Movement Disorders Program, Barrow Neurological Institute, Phoenix Children's Hospital
Departments of Child Health, Neurology, and Cellular & Molecular Medicine and Program in Genetics, University of Arizona College of Medicine - Phoenix Children's Hospital

Michael E. Msall, MD
Email: mmsall@peds.bsd.uchicago.edu
Affiliation: University of Chicago Kennedy Research Center on Neurodevelopmental Disabilities, Chicago IL USA

Garey Noritz, MD
Email: Garey.Noritz@NationwideChildrens.org
Affiliation: Department of Pediatrics, Nationwide Children's Hospital and The Ohio State University, Columbus OH, USA

Deepa S. Rajan, MD
Email: rajands@upmc.edu

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Affiliation: Department of Pediatrics, Division of Child Neurology, UPMC Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA

Bhooma R. Aravamuthan, MD, DPhil
E-mail: aravamuthanb@wustl.edu
Affiliation: Washington University School of Medicine, Department of Neurology, Division of Pediatric Neurology, St. Louis, MO, USA

Abstract

Cerebral palsy (CP) neurologic care and research efforts typically focus on children. However, most people with CP are adults. Adults with CP are at increased risk of new neurologic conditions, like stroke and myelopathy, that require ongoing neurologic surveillance to distinguish them from baseline motor impairments. Neurologic factors could also contribute to the motor function decline, chronic pain, and chronic fatigue that are commonly experienced by adults with CP. Based on a systematic literature review, we suggest: 1) guidelines for neurologic surveillance and neurologist referral; and 2) clinical research questions regarding the evolving neurologic risks for adults with CP.

Introduction

Cerebral palsy (CP) is a clinical descriptor for a non-progressive motor disability due to a disturbance in the developing fetal or infant brain[1]. Approximately 2 in 1000 live-born infants develop CP, making it one of the most prevalent lifelong disabilities[2]. Although frequently regarded as a pediatric disorder, the majority of people with CP are now adults[3]. However, clinical care and research efforts tend to focus on the pediatric population. This is despite the many medical and psychosocial needs of the adult population with CP, including their changing, and in many cases worsening, neurologic status[4, 5].

CP is non-progressive by definition[1]. However, though the initial neuropathology does not worsen, CP is a not a static disorder:

- Many adults with CP will worsen one Gross Motor Function Classification System (GMFCS) level as they age (Table 1), with many losing their ability to walk independently[4, 6].
- Compared to others the same age, adults with CP have a higher risk of new onset neurologic issues, including stroke and myelopathy[7-9].
- CP could functionally enhance later age-related neurodegenerative changes, though we lack data on relative rates of dementia and cognitive disorders in this population[10, 11].
- Existing neurologic symptoms for those with CP (e.g. epilepsy, spasticity, and dystonia) may change in adulthood or remain un-diagnosed or under-treated.
- New symptoms with possible neurologic etiologies are common in adults with CP, such as chronic pain or chronic fatigue[5].

These phenomena necessitate detailed neurologic surveillance, particularly since new motor impairments can be difficult to distinguish from long-standing impairments without rigorous tracking of the neurologic exam and neuromotor functional status.

Here, we outline the neurologic concerns affecting people with CP as they age, including neurologic symptoms that may emerge or change in adulthood. We provide the available evidence regarding these symptoms in adults with CP using a systematic literature review, with the caveat that data regarding the cause, prevalence, and treatment options for these symptoms are lacking and would benefit from research efforts that could be neurologist-driven. Based on this literature review, we advocate for neurologist involvement in the care and neurologic surveillance of adults with CP and additionally highlight the primary areas of neurologic research needed in this population (Table 2).

Methods

This qualitative systematic review is conducted in accordance with the Preferred Reporting for Systematic Reviews and Meta-Analysis (PRISMA) statement[12]. We performed a comprehensive search of PubMed and Web of Science to include articles from January 1, 1950 to May 31, 2020 for descriptions of neurologic conditions present in adults with CP (search terms and the Complete Reference List are available at https://github.com/sarah-e-smith/CP-Review). We also reviewed references already familiar to the authors for eligibility. The number of references included and excluded at each screening stage are shown in a PRISMA-style flowchart (Figure 1). Eligible studies were: (1) Written in English, (2) Studied adults with CP, and (3) Were not editorials or redundant of other included studies. Meta-analyses, abstracts and reviews were included if they met the above criteria.

Results

A total of 2621 records were screened with 109 articles meeting inclusion and exclusion criteria as summarized below, with most salient articles cited here and all sources presented in the Complete Reference List (Figure 1).

Evaluation of CP etiology

CP has often been viewed in the context of acquired injury[13]. However, non-acquired etiologies of CP (e.g. brain structural malformations and other genetic etiologies) are being increasingly identified and require clear differentiation from CP mimics which, unlike CP, present with a progressive motor phenotype[14].

The increasing availability of genomic technologies add a rapidly changing dimension to CP diagnosis. CP susceptibility genes have been recently identified that contribute an increased risk of premature birth, perinatal events, and CP itself[15, 16]. Although ascertainment criteria and variant assessment have varied, at least 14% of individuals with CP have an identifiable genetic etiology[17].

Unlike CP in childhood , there is a notable lack of systematic characterization of CP etiologies in adults. Given the recent progress in genetic CP characterization, genetic testing may not have been offered to many adults carrying a CP diagnosis. This lack of etiological identification gains significance particularly as adults with CP enter their childbearing years. Establishing whether a genetic etiology exists can be critical for family planning, prognostication, and management. Neurologists are in a unique position to accurately phenotype adults with CP and could therefore be ideally suited to revisit a comprehensive diagnostic evaluation for adults with CP, including genetic testing[18].

Stroke

Strokes occur more frequently in adults with CP. In a large population-based study from 2015, age-adjusted prevalence rates for stroke are 4.6% in adults with CP, and 2.3% among matched controls[19]. Noting that adults with CP have elevated rates of mortality overall, they also have more than double the rate of death from cerebrovascular disease compared to population-wide rates[20].

Risk factors such as increased rates of hypertension, diabetes and hyperlipidemia compared to the general population have been proposed to play a role in the increased prevalence of stroke among adults with CP[19, 21-23]. However, even after adjusting for age, sex, demographics, diabetes, hypertension, coronary artery disease, dyslipidemia and chronic liver disease, the adjusted stroke hazard ratio is approximately 2 times greater in adults with CP[9]. The etiologies, distribution and presentation of strokes (e.g. ischemic vs. hemorrhagic, thrombotic vs. embolic) in adults with CP are not well characterized. This data is necessary to help understand the pathological underpinnings of stroke risk in CP and to develop the best strategies for managing stroke risk in this population.

Myelopathy

Adults with CP are at increased risk of myelopathy as they age, particularly cervical and lumbar, due to canal narrowing and cord compression from spondylosis (associated with osteophyte formation, ligamentum flavum hypertrophy, and age related disc degeneration and herniation[24]). Radiological studies revealed that adults with CP and dystonia exhibited 8 times the frequency of cervical disc degeneration, spondylosis, and significant canal narrowing compared to control subjects[7, 8]. In a prospective case-control study hypothesizing that cervical spondylosis may be hastened by the mechanical strain of cervical dystonia, 31% of adults with dystonic CP developed cervical myelopathy, all after age 36[25]. Increasing age and greater severity of cervical dystonia were associated with a higher risk of cervical myelopathy, with the authors suggesting that adults with dystonic CP should be regularly screened for cervical myelopathy starting at age 30[25]. However, adults with CP without dystonia still develop myelopathy. CP is associated with a higher risk of cervical myelopathy than focal cervical dystonia, suggesting that cervical dystonia is not the only risk factor for myelopathy[26]. Supporting this point, a recent study found that 7.5% of adults with spastic cerebral palsy had symptomatic cervical spinal stenosis[27]. Thus some orthopedists recommend screening all adults

with CP over age 50 for cervical spinal stenosis with cervical spine X-rays[28]. Importantly, neurologic screening recommendations for spondylotic myelopathy in this neurologically complex population are lacking, which is problematic given that spondylotic myelopathy can often yield subtle symptoms even in otherwise healthy individuals[24]. In addition to greater clinical attention to myelopathy screening in individuals with CP, improving outcomes will require further research into why and to what extent various manifestations of CP associate with myelopathy.

Loss of Mobility

The majority of adults with CP are ambulatory (58% overall, 73% of those without comorbid intellectual disability)[5]. However, the average adult with CP begins experiencing deterioration in walking ability starting by age 35[29]. Peak mobility for people with CP is in the mid- to late-teens[30].

Gross motor functional decline occurs earlier in adults with CP than in the general population[4, 31]. Over 1/3 of adults with CP will worsen by one GMFCS level during adulthood[32]. A large longitudinal study followed cohorts of adults with CP aged 20, 40 and 60 years for 15 years and documented their functional status[33]. Although 39% of adults could walk unassisted at age 20, only 25% could do so at age 60. A substantial decline in mobility occurred over 15 years in all age cohorts. The risk of mobility deterioration increases with age[29, 30, 34].

Gross motor functional decline tends to associate closely with other symptoms of CP, such as pain and fatigue. In a 7-year longitudinal cohort study, people with deterioration in gross motor ability over that period reported greater levels of pain and fatigue than those maintaining their functional status. Notably, adults with better functional status appear to be less at risk for early decline. For example, deterioration occurs more quickly in those with bilateral rather than unilateral distribution of CP, and in those who experienced developmentally delayed walking[34].

Better motor functional ability (i.e. GMFCS level I versus level III) is also associated with a later age of peak mobility[30, 34].

The reasons for this gross motor functional decline are unclear but could be precipitated by a combination of emerging myelopathy, accumulation of cerebrovascular injury, under-treated dystonia or spasticity, increasing pain and fatigue, lack of accessible recreation and fitness facilities, poor levels of overall fitness, and decreased access to medical and physical therapy in adulthood[5, 22, 35, 36]. Many of these causes would benefit from neurologic evaluation, management, and care coordination, in addition to further research into which factors are most pertinent.

Spasticity

Spasticity, characterized by velocity-dependent increased tone in response to passive stretch, is the most common motor manifestation of CP[2]. However, the appearance and treatment of spasticity in adults with CP are grossly understudied.

The evolution of spasticity over time has only has been studied across childhood, though without a clear differentiation in outcomes between different distributions of spasticity (i.e. diplegia, hemiplegia, triplegia, quadriplegia). Assessment of spasticity using the Modified Ashworth Scale (MAS) has demonstrated that the highest scores (associated with more severe spasticity) occur in the plantar flexors at age 4-5 years with subsequent stabilization to minimal improvement over time at least through age 15[37, 38]. Noting poor interrater reliability and the subjective nature of the MAS, another study used objective isokinetic dynamometry to demonstrate increased passive torque in the knee flexors with increasing age (between 7 and 14 years old)[39]. Therefore, it is possible that spasticity evolves differently in different muscle groups (e.g. plantar flexors versus knee flexors) at least across childhood. Changes in spasticity into adulthood have yet to be studied rigorously, but the fact that spasticity evolves at all in CP, which is often erroneously viewed as a static disease process, warrants further longitudinal

study of spasticity across all age groups. Of note, complicating the characterization of the natural evolution of spasticity in adults with CP are increased risks of stroke and myelopathy in this population, contributing new etiologies of spasticity as people with CP age.

Dystonia

Dystonia, a movement disorder characterized by overflow muscle activation triggered by voluntary movement[40], is a common motor manifestation of CP in both children and adults and often co-occurs with spasticity[41]. Dystonia patterns and pharmacologic treatments in adults with CP, particularly older adults, are relatively understudied.

Greater evidence exists for surgical treatments. Both intrathecal baclofen pump implantation and deep brain stimulation (DBS) of the globus pallidus pars interna have been reported as effective treatments for some adults with CP and medically-refractory dystonia[42, 43]. Studies suggest that DBS may best benefit those with milder dystonia and minimal other motor manifestations of CP[44, 45]. In more severely affected individuals, Burke-Fahn-Marsden scores of dystonia severity are not improved with DBS, though subjective symptom ratings are[46]. A recent review argues that DBS is a promising option for treating CP-associated dystonia when other treatments have failed, and ideal candidates should be identified and implanted as early as possible for maximum benefit[43]. This has been best demonstrated in children where the proportion of life lived with dystonia correlates negatively with DBS efficacy[47].

Noting the relatively recent application of DBS for dystonia in CP, many young adults with dystonic CP who may still be DBS candidates may not have been evaluated for DBS. Early recognition of dystonia is critical for appropriate institution of surgical treatments. However, dystonia in CP and is often misdiagnosed as spasticity or underdiagnosed[48]. Therefore, adults with CP who are functionally limited by their dystonia may never have received a dystonia diagnosis. Therefore, neurologic evaluation for dystonia in adults with CP could be helpful for determining candidacy for surgical intervention, optimizing pharmacologic dystonia treatment,

and also establishing the diagnosis of dystonia itself. Optimizing care will require characterizing the patterns of dystonia in adults with CP and studying the comparative effectiveness of dystonia treatments in adults with CP.

Dementia

Whether adults with CP are at greater risk for developing dementia remains an unsolved and crucial question in the field. Few studies directly address dementia prevalence in CP. A study of over 1000 adults with CP and matched controls suggest that those with CP and co-morbid intellectual disability or epilepsy have a 7-12 fold increased risk of dementia[10]. Furthermore, functionally detrimental new memory loss is reported by 25% of adults with CP[11]. Therefore, regular cognitive screening can be useful for epidemiologic characterization and also to detect early signs of dementia in this potentially at-risk population.

The variable association of CP with the Alzheimer's disease risk allele apolipoprotein ε4 may or may not support an association between CP and dementia. This association was first observed in a small study (n=40) in 2000, suggesting a four-fold increased risk of CP in the general population with the ε4 allele compared to those without it, with no significant difference for the ε2 or ε3 alleles[49].

Larger follow-up studies have garnered conflicting results. A 2007 study found that both the ε4 allele, which confers increased risk for Alzheimer's disease, and the ε2 allele, which confers decreased risk, occur at higher frequencies in adults with CP than those without[50]. However, no association of apolipoprotein E genotype and CP was found in a large population-based study of Caucasian infants[51]. A 2010 cross-sectional study found an increased risk of CP in those with the ε2 allele, but no increased risk with ε4[52].

Despite this lack of consensus regarding associations with the apolioprotein E genotype, it remains worth investigating the prevalence and characteristics of dementia in adults with CP

noting that their higher burden of cerebrovascular disease compounds upon long standing brain injury. Future research on the association between dementia and CP should involve detailed characterization of subjects' education level, brain imaging patterns of injury and atrophy, and incidence of co-morbid conditions like epilepsy, autism, and intellectual disability, all factors which have not been assessed simultaneously, let alone longitudinally, in adults with CP.

Epilepsy

Epilepsy affects 30-40% of children with CP[2, 53]. The risk of epilepsy is increased in children with worse functional status or those with co-morbid intellectual disability[53]. In adults with CP, epilepsy is less well characterized. A retrospective cohort study of adults with CP and co-morbid epilepsy found that half achieved seizure remission (seizure freedom for at least 2 years) during the 35-year study period. The median age of remission was 11 years old, but for many, remission occurred in adulthood. Subjects in this study who were taken off of anti-epileptic drugs (AEDs), the majority of whom had focal brain lesions, remained seizure free following AED discontinuation. Therefore, ongoing re-evaluation of the need for AEDs in adults with CP achieving seizure remission should occur on both a clinical and research basis[54].

Though it has been suggested that co-morbid epilepsy may increase the risk of dementia in adults with CP[10], it is unknown whether the incidence, severity, or duration of epilepsy modifies the risk of any other neurologic or functional outcomes in adults with CP. The interaction between epilepsy and CP in adults, therefore, requires further research.

Chronic Fatigue and Sleep Disorders

Chronic fatigue presents a common problem as adults with CP age and remains one of the most disruptive and undertreated symptoms for this population. A recent meta-analysis estimated a mean fatigue severity score of 4.1 (on a scale of 1-7, with 4 or greater indicating fatigue) among adults with CP[5]. This average may underestimate the actual fatigue burden in

this population, as most studies query young adults and fatigue in CP increases with age[55, 56]. Still, even adults with CP in their 20s, 30s and 40s experience significantly more fatigue than typically-developing age-matched adults[11, 57, 58]. Estimates of fatigue prevalence ranges from 64% to nearly all adults with CP[5, 11, 55]. Chronic fatigue correlates with lower life satisfaction and significant worry in this population[56, 59].

The factors contributing to chronic fatigue in CP are unclear, and the methods by which this fatigue can be optimally addressed are similarly undefined. Disproportionately high rates of depression and anxiety in adults with CP could manifest as fatigue[60]. Fatigue appears to associate highly with other adverse symptoms of CP, including pain and poor walking ability[59]. Although fatigue is present across all functional statuses, fatigue is worse on average for those with greater gross motor impairment[58]. Despite this, an intervention that improves motor function, childhood selective dorsal rhizotomy, does not affect fatigue or pain levels once these children reach adulthood[61]. The current literature also presents a complicated story with regard to the role of physical activity in fatigue. Some surveys show an association of fatigue and inactivity[62]. Higher BMI and larger waist circumference correlates significantly with fatigue severity[62]. A pilot study on the effect of an exercise program in adults with CP showed a mild but significant benefit on the levels of fatigue[63]. In apparent contradiction, adults with CP report both reducing physical activity (59.5%) and participating in exercise (13.5%) as helpful interventions for reducing their fatigue[55].

Disordered sleep may also be contributing to chronic fatigue in adults with CP. About 1 in 4 children with CP exhibit disordered sleep, as judged by an abnormal score on the sleep disorder scale for children (SDSC), with an even greater risk for children with poor gross motor functioning or co-morbidities such as epilepsy[64]. Less evidence exists for the adult population. One recent meta-analysis suggests that, although the overall rate of sleep disturbance in adults with CP does not significantly differ from those without CP, the degree of sleep disturbance worsens with increasing gross motor functional impairment[65]. Another study of adults with CP

found that particularly high rates of sleep disturbance are found in individuals reporting the highest levels of chronic pain, presenting a possible area of intervention[66]. More specific data on the types of sleep disturbance (e.g. sleep-wake transition disorders, parasomnias, insomnia) has been collected in children, but has not been well studied in adults with CP[64].

Because of the paucity of interventional studies addressing fatigue reduction in adults with CP, an individualized approach is required to guide clinical decision making. Treating other neurologic symptoms of CP, such as spasticity, dystonia, myelopathy, and cerebrovascular disease risk factors, may improve fatigue by improving functional status. Physical and occupational therapy will likely prove to be beneficial if therapists are able to increase fitness and physical activity while avoiding exhaustion. Evaluating and treating sleep disorders may also prove beneficial, but these areas require further research[65].

Pain

Adults with CP commonly experience pain, with two 2020 meta-analyses estimating an overall pain prevalence of 65-70%[5, 67]. Numerous studies find that adults with CP experience significantly more pain than those without CP[5]. Yet, the majority of adults with CP and pain do not seek pain treatment[68]. As a result, there is a huge unmet need for pain relief among this population[69].

Despite a wealth of prevalence and associative data, the causes of pain in this population remain unclear. It is well established that adults with CP are at higher risk of osteoarthritis, osteoporosis, joint contractures and related musculoskeletal issues[19]. Many of these issues are highly associated with pain in adults with severe spastic CP, but are also found in the majority without pain[70]. Moreover, adults with CP exhibit an increased prevalence of other types of pain as well, such as abdominal pain and pain associated with bowel/bladder dysfunction[67]. Central pain syndromes, possibly due to the high prevalence of thalamic injury particularly in those with dystonic CP[71], may contribute to the high pain burden in adults with

CP[72]. In support of a central pain etiology, adults with CP have demonstrated mechanical hyperalgesia[72] and shown improvement in whole body pain following unilateral thalamotomy in a small study[73].

More research is required on which treatments are effective for pain in this population and how best to increase access to care. Surveys indicate that the majority of adults with CP are using conservative measures, such as NSAIDS and stretching, rather than opioids, baclofen, benzodiazepines or invasive treatments[69]. Conservative measures did not improve pain over a 2 year period, but were associated with pain not worsening[69]. Common treatment regimens for central pain syndromes have not been explored in CP, and is an area of needed study. In children with severe dystonic CP, high dose gabapentin can reduce pain and decrease dystonia[74], though this has not been systematically evaluated in adults. For adults with severe spasticity, intrathecal baclofen significantly reduces pain[75]. However, other anti-spasticity treatments such as botulinum toxin and selective dorsal rhizotomy have variable impacts on adulthood levels of pain[61, 76]. Therefore, assessment for functionally limiting pain should, in part, inform decisions regarding spasticity and dystonia treatments. Further research into which interventions have the greatest success at alleviating pain and what the underlying causes are in this population will also be crucial.

Discussion

Aging with CP is accompanied by new and changing neurologic symptoms including increased risk and/or earlier ages of stroke, myelopathy, loss of mobility, dementia, pain, and fatigue. Co-existing neurologic symptoms like spasticity, dystonia and epilepsy often require on-going neurologist-guided management. Further research is required on all of these neurologic symptoms in adults with CP, certainly with regards to modifiable risk factors and treatments, but also often with regards to symptom prevalence and characteristics. We outline suggestions for

how neurologists, adults with CP and researchers can work together to address these problems both at the individual and population level (Table 2).

Neurologic symptoms in adults with CP, particularly if inadequately treated, could contribute to earlier functional decline. Adults with CP should be neurologically screened, at minimum, with any signs of functional decline, but ideally before functional decline occurs. In sum, adequate medical treatment for the adult person with CP requires ongoing care from a neurologist (Figure 2).

This review and much of the research on adults with CP has focused on gross motor function. However, functional decline may take many forms across many domains. In addition to the GMFCS, four other validated classification systems exist to categorize function in individuals with CP in the fine motor, vision, communication, and eating and drinking domains (Table 1) [77-80]. These classification systems also merit inclusion by neurologists when tracking functional status in this population, both clinically and for research studies.

Recent Advances

Clinicians and researchers are engaged in multiple lines of inquiry to improve the treatment of adults with CP. Some of this is extending the use of childhood interventions to adult patients. For instance, outcomes for adults undergoing selective dorsal rhizotomy, injection of Botulinum A Toxin, and orthopedic surgery have been reported[81-83]. Improving access to and acceptance of exercise by adults with CP has been the subject of several studies and clinical projects[84, 85]. As highlighted throughout this article, the rigorous tracking of neurologic outcomes is an area of significant need.

In contrast to children with CP, adults with CP are rarely cared for by multidisciplinary teams in large centers, so health services researchers have used administrative data sets to gather large enough samples to estimate the prevalence of comorbidities such as diabetes and hypertension[23]. Attention has now been turned to how these comorbidities interact to produce

loss of function and increase mortality[86, 87]. Direct neurological assessment of adults with CP can valuably expand on this literature.

An encouraging feature of current research in adults with neurodevelopmental disabilities like CP is the inclusion of the adults themselves in planning and executing the studies, from choosing the study priorities[88], attention to the patient lived experience[89], and co-authoring reports[90]. Neurologists and neuroscientists should aim to continue this focus.

Future Directions

In addition to neurologic care, adults with CP require care from other informed providers. Neurologists should partner with physical medicine and rehabilitation specialists, physical therapists, occupational therapists, orthopedists and others to help manage the multiple symptoms that can emerge in adults with CP. Neurologists should also partner with primary care physicians to ensure adequate detection and care of co-morbid medical conditions. Numerous studies over the last 10 years have found that adults with CP are at increased risk of multiple non-communicable diseases including diabetes, hypertension, asthma, heart disease, emphysema, and arthritis[23], many of which can contribute to the increased risk of stroke, pain, and fatigue observed in this population. Though rates of depression do not appear to be as high as in those with adult-onset neurological disorders such as multiple sclerosis[91], clinicians should also be aware that adults with CP are 50% more likely than their non-disabled peers to experience anxiety and depression, and more likely to develop other psychiatric diseases[60]. Interestingly, the increased prevalence of depression in adults with CP seems largely driven by individuals without intellectual disability, suggesting this population in particular may benefit from the care of a psychiatrist[92]. Ideally, integrated multidisciplinary service models should be created to coordinate care delivery from these providers, as has been done for other chronic neurologic diseases of adulthood.

Neurologists should also be aware that a CP diagnosis requires association with a CP etiology. Determining the etiology of a person's CP can be critical for family counseling, prognostication, screening for associated co-existing conditions and treatment. As of now, the epidemiology of CP etiologies in adults has not been well-described and it is possible that many adults with CP have not had formal investigation of their CP etiology.

As individuals with cerebral palsy age, they have greater needs for health care but have less access to it. Many report that they do not see a specialist after high school, despite the significant neurologic issues noted here and their increased risk of other chronic diseases[93]. Pediatric neurologists are generally not trained in adult medical or psychosocial issues[94]. Adult neurologists have not been responsible for diagnostic evaluation of pediatric diseases and have limited training in how pediatric onset disability affects adult physiology[95]. Fortunately, there are a growing number of clinicians and clinical settings where the issues and concerns of adult patients with pediatric onset disabilities are being addressed, and there is a growing body of knowledge to aid these practitioners in designing best practices for monitoring, prevention, and care. Additional training at every level of neurologic education is critical to increase neurologist awareness about these issues. Practice guidelines and seminars at national conferences will increase awareness, at least in generating referral to the developing specialty centers. Telemedicine opens up the opportunity for access to physicians and other caregivers with expertise in areas where they may not be available in person. Organizations like the Cerebral Palsy Research Network also promote goal-driven research partnerships between practitioners and the broad community of adults with CP, which can further research and care guidelines in a patient-centered way[88]. These and other interventions focusing on increasing health care access for adults with CP are critical for preventing and treating the complications discussed in this review.

We still know little about the causes of many neurologic symptoms in adults with CP. Detailed prospective motor phenotyping and neurologic surveillance will be required to begin

understanding these numerous, often ignored, challenges faced by adults with CP. Neurologists are critical for this effort.

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Table and Figure Titles and Legends

Table 1 Descriptions of validated functional classification systems. GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System; CFCS, Communication Function Classification System; EDACS, Eating and Drinking Ability Classification System; VFCS, Visual Function Classification System. Table adapted from reference[79]

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart

Figure 2. Key summary points from a systematic review of the literature on neurologic concerns in adults with CP

Table 2. Proposed Actions for Neurologists, Adults with Cerebral Palsy and Researchers Regarding Potential Neurological Concerns in Adults with CP. See Supplemental Table 1 for extended version of table.

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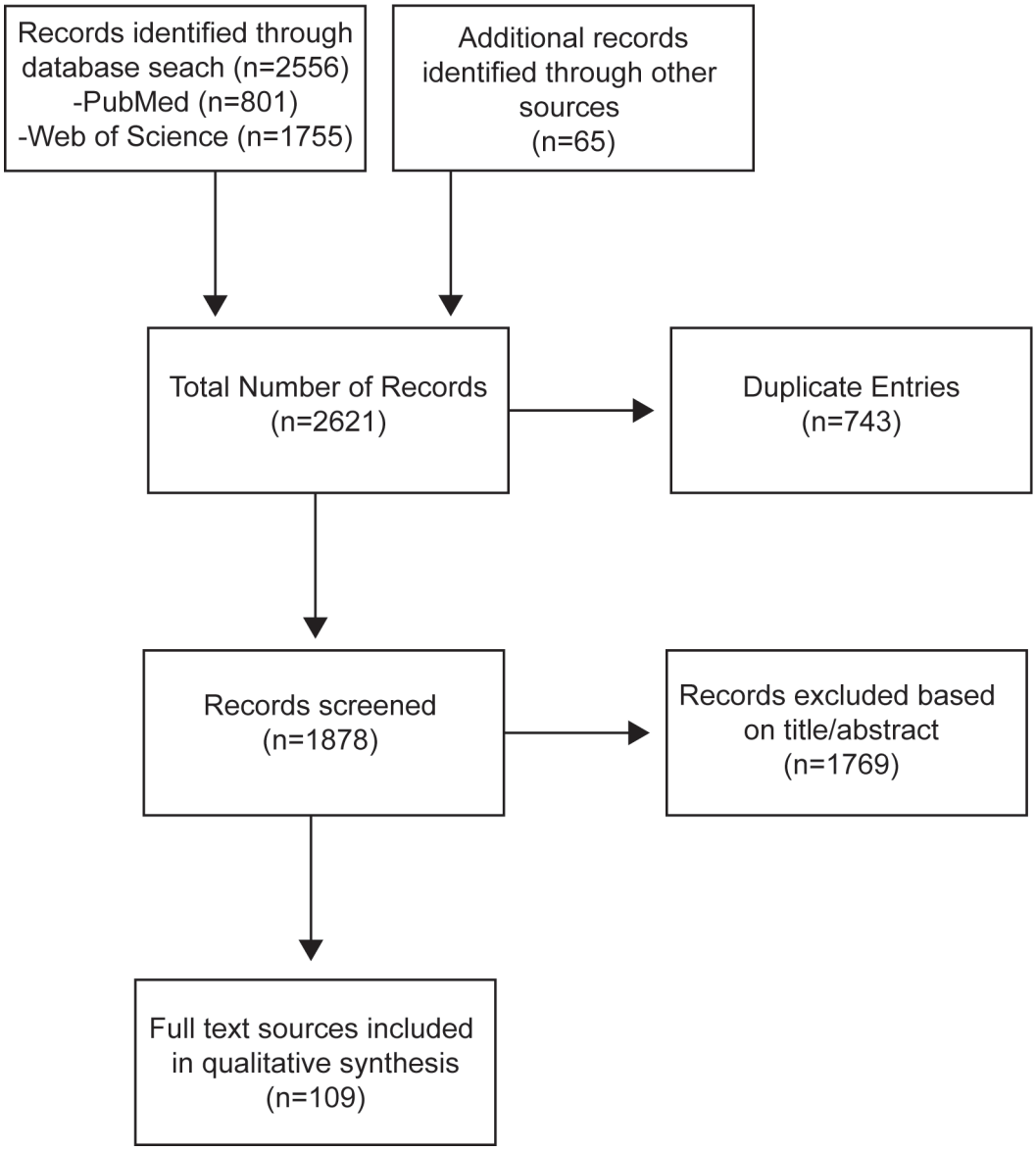

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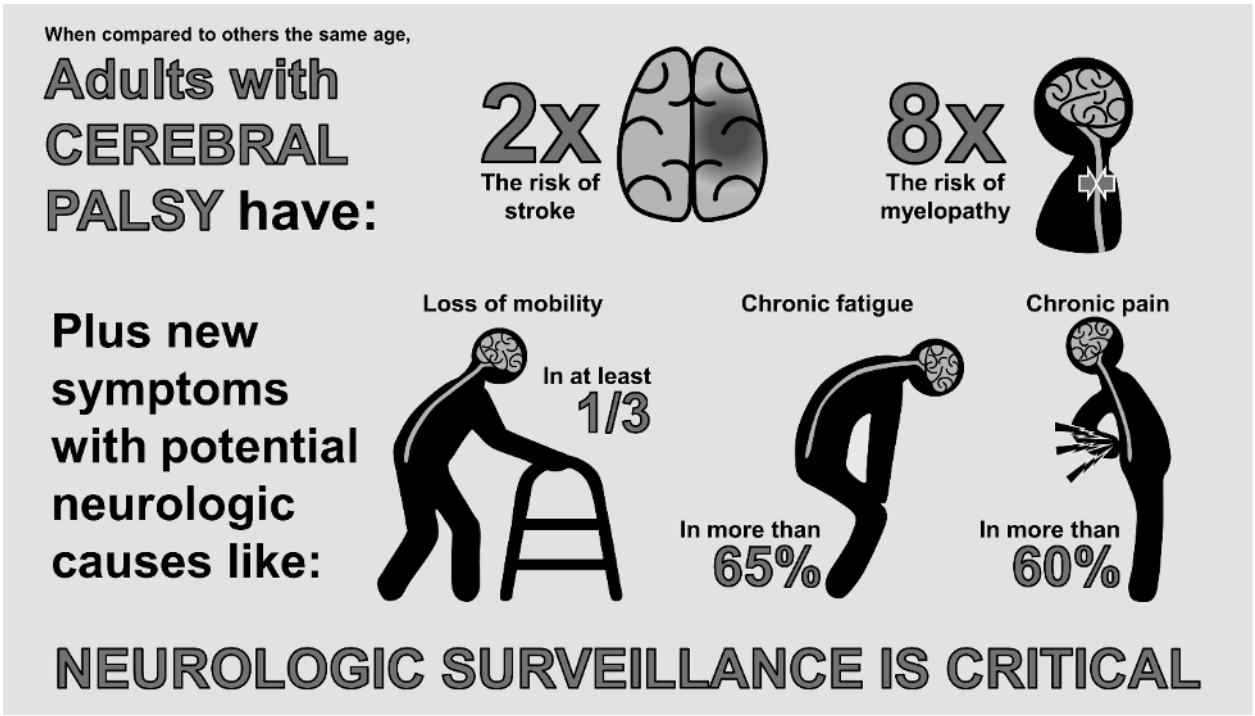

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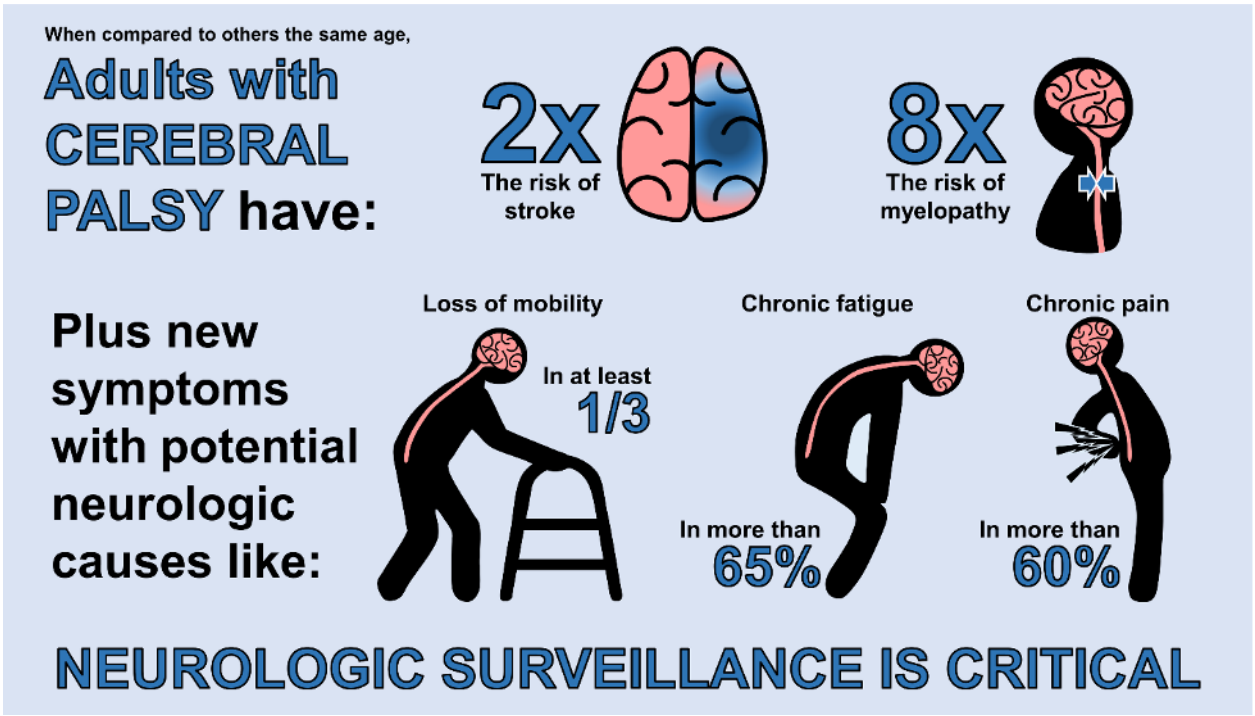

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Level	GMFCS	MACS	CFCS	EDACS	VFCS
I	Walks without limitations	Handles objects easily and successfully	Sends and receives with familiar and unfamiliar partners effectively and efficiently	Eats and drinks safely and efficiently	Uses visual function easily and successfully in vision-related activities
II	Walks with limitations	Handles most objects but with somewhat reduced quality and/or speed of achievement	Sends and receives with familiar and unfamiliar partners but may need extra time	Eats and drinks safely but with some limitations to efficiency	Uses visual function successfully but needs self-initiated compensatory strategies
III	Walks using a hand-held mobility device	Handles objects with difficulty; needs help to prepare and/or modify activities	Sends and receives with familiar partners effectively, but not with unfamiliar partners	Eats and drinks with some limitations to safety; there may be limitations to efficiency	Uses visual function but needs some adaptations
IV	Self-mobility with limitations; may use powered mobility	Handles a limited selection of easily managed objects in adapted situations	Inconsistently sends and/or receives even with familiar partners	Eats and drinks with significant limitations to safety	Uses visual function in very adapted environments but performs just part of vision-related activities
V	Transported in a manual wheelchair	Does not handle objects and has severely limited ability to perform even simple actions	Seldom effectively sends and receives, even with familiar partners	Unable to eat and drink safely – tube feeding may be considered to provide nutrition	Does not use visual function even in very adapted environments

Table 1. Descriptions of validated functional classification systems. GMFCS, Gross Motor Function Classification System; MACS, Manual Ability Classification System; CFCS, Communication Function Classification System; EDACS, Eating and Drinking Ability Classification System; VFCS, Visual Function Classification System. Table adapted from reference[79]

	For Neurologists Caring for Adults with Cerebral Palsy	For Adults with Cerebral Palsy and/or their Caretakers	For Clinical Researchers
Etiology 13,15,18	-Obtain a baseline brain MRI to look for residua of acquired injury or other structural brain malformations that could have caused CP -Consider genetic testing if normal brain MRI, no spasticity, late onset of symptoms, family history of CP, and/or no clear acquired source at birth	-If you do not know why you have CP, ask your doctor. If your doctor does not know, ask for a referral to a specialist (like a neurologist) who can help evaluate you for the cause of your CP.	-What is the spectrum of etiologies of CP in adults? -How common are genetic etiologies of CP in adults? -If a genetic etiology of CP is identified in adulthood, how often does that change management?
Stroke 19, 21-23	-Comprehensively document the patient's baseline neurologic exam so changes can be more easily discerned -Educate patients with cerebral palsy about their increased risk of stroke and signs of stroke -Consider a Brain MRI in patients with new functional decline, particularly for stepwise declines	-Work with your doctors to ensure that chronic medical conditions including high blood pressure, high cholesterol, and diabetes are well-controlled -Seek immediate medical attention for any sudden decline in your typical level of functioning	-What are the etiologies and distribution of strokes in individuals with CP (e.g. embolic/large vessel vs. lacunar/small vessel)? -Does tight control of modifiable risk factors for stroke (e.g. hypertension, dyslipidemia) normalize stroke risk in individuals with CP?
Myelopathy 24, 25, 27, 28	-Ask patients about new urinary retention/incontinence, new hand numbness/weakness, new difficulty with ambulation, decreased leg strength, and increased leg tone -Monitor the neurologic exam longitudinally, monitoring closely for increasing lower extremity spasticity, consider spinal MRI in patients with subacute functional motor decline	-New hand numbness or weakness, problems going to the bathroom, or increased difficulty with moving your legs could be early signs of spinal cord compression: seek neurologic care if these occur over a period of weeks; seek emergency care if sudden	-Are rates of myelopathy different between adults with CP with cervical dystonia, dystonia in other locations, athetosis or no/minimal dystonia or athetosis? -What is the appropriate screening protocol for spine imaging?
Mobility Loss 5, 22, 35, 36	-Monitor the neurologic exam longitudinally for worsening spasticity, dystonia, pain or weakness, and intervene ideally before these symptoms cause motor function decline	-Losing previously held abilities to move around is not a natural part of aging – seek neurologic care if this occurs	-What are the contributing etiologies for mobility loss in adults with CP? -What interventions slow functional loss?
Spasticity and Dystonia 41-43, 48, 61, 75, 76	-Be aware of the patient's baseline tone so that changes can be diagnosed and treated. Possible causes of symptom change include myelopathy, stroke sequelae, progressive motor disability suggestive of a CP mimic or evolving baseline CP symptoms	-Seek neurologic care if your increased muscle tone or abnormal movement is either worsening or becoming a problem for doing the things you want to do	-What are the severity and distribution patterns of dystonia and spasticity with aging in CP? -Are there tone treatments in childhood that have better adult outcomes or treatments that are particularly effective in adults?
Dementia 10, 11	-Ask patients about memory loss. Consider a screening test. -Patients with CP and epilepsy or intellectual disability may warrant closer cognitive screening, as they may be at increased risk of dementia	-New memory loss, especially if it is bothersome in your daily life, should prompt neurologic evaluation	-Accounting for education level, imaging patterns of injury, polypharmacy, and co-morbid conditions, do adults with CP have higher rates of dementia compared to age-matched individuals?
Epilepsy 54	-Re-evaluate need for anti-epileptic medications in seizure-free patients -Refer patients with refractory epilepsy for surgical evaluation, particularly if they have a known brain injury or malformation	-If you have seizures, seek neurologic care -If you have been seizure free for years on medication, seek neurologic care to see if you could wean off your medications	-What happens to seizure frequency as adults with CP age? -What percentage of adults with CP can be successfully weaned off of AEDs?
Chronic Fatigue and Pain 5, 11, 55, 66, 67, 70	-Ask patients about these extremely common and disruptive symptoms. -Fatigue and pain may derive from neurologic problems such as spasticity and dystonia, or psychiatric problems such as depression or anxiety, so address any root contributors.	-If fatigue or pain is negatively influencing your life, discuss with your PCP and consider seeing a neurologist. Better control of your CP symptoms may improve your fatigue and pain.	-Is pain more common in adults with CP with thalamic injury? -What are the most effective pain treatments for adults with CP?

Table 2. Proposed Actions for Neurologists, Adults with Cerebral Palsy and Researchers Regarding Potential Neurological Concerns in Adults with CP. See Supplemental Table 1 for extended version of table.